ORIGINAL ARTICLE

Liberal or Restrictive Transfusion Strategy in Aneurysmal Subarachnoid Hemorrhage

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ABSTRACT

BACKGROUND

The effect of a liberal red-cell transfusion strategy as compared with a restrictive strategy in patients during the critical care period after an aneurysmal subarachnoid hemorrhage is unclear.

METHODS

We randomly assigned critically ill adults with acute aneurysmal subarachnoid hemorrhage and anemia to a liberal strategy (mandatory transfusion at a hemoglobin level of ≤10 g per deciliter) or a restrictive strategy (optional transfusion at a hemoglobin level of ≤8 g per deciliter). The primary outcome was an unfavorable neurologic outcome, defined as a score of 4 or higher on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability) at 12 months. Secondary outcomes included 12-month functional independence as assessed with the Functional Independence Measure (FIM; scores range from 18 to 126) and quality of life as assessed with the EuroQol five-dimension, five-level (EQ-5D-5L) utility index (scores range from −0.1 to 0.95) and a visual analogue scale (VAS; scores range from 0 to 100); on each assessment, higher scores indicate better health status or quality of life.

RESULTS

A total of 742 patients underwent randomization at 23 centers. The analysis of the primary outcome at 12 months included 725 patients (97.7%). An unfavorable neurologic outcome occurred in 122 of 364 patients (33.5%) in the liberal-strategy group and in 136 of 361 patients (37.7%) in the restrictive-strategy group (risk ratio, 0.88; 95% confidence interval [CI], 0.72 to 1.09; P=0.22). The mean (±SD) FIM score was 82.8±54.6 in the liberal-strategy group and 79.8±54.5 in the restrictive-strategy group (mean difference, 3.01; 95% CI, −5.49 to 11.51). The mean EQ-5D-5L utility index score was 0.5±0.4 in both groups (mean difference, 0.02; 95% CI, −0.04 to 0.09). The mean VAS score was 52.1±37.5 in the liberal-strategy group and 50±37.1 in the restrictive-strategy group (mean difference, 2.08; 95% CI, −3.76 to 7.93). The incidence of adverse events was similar in the two groups.

CONCLUSIONS

In patients with aneurysmal subarachnoid hemorrhage and anemia, a liberal transfusion strategy did not result in a lower risk of an unfavorable neurologic outcome at 12 months than a restrictive strategy. (Funded by the Canadian Institutes of Health Research and others; SAHARA ClinicalTrials.gov number, NCT03309579.)

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*A complete list of participating sites and investigators for the SAHARA trial is provided in the Supplementary Appendix, available at NEJM.org.

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Subarachnoid hemorrhage from intracranial aneurysm rupture is a severe and life-threatening condition. It is a notable cause of early death and loss of productive life years,[1] with case fatality rates ranging from 8.3 to 66.7%.[2] Subarachnoid hemorrhage affects a young and predominantly female population. The clinical course is complicated by early and delayed neurologic insults. Among survivors, fewer than one third have full recovery,[2] and a substantial proportion endure long-term effects that lead to dependent living.[3]

Anemia occurs in more than 50% of patients with subarachnoid hemorrhage and is associated with worse clinical outcomes.[4,5] By reducing oxygen delivery, anemia may exacerbate the early and delayed neurologic insults that follow aneurysm rupture (e.g., delayed cerebral ischemia) and are major contributors to poor neurologic recovery.[6,7] Although red-cell transfusion may enhance the delivery of cerebral oxygen,[8] whether this improvement is associated with improved clinical outcomes is not known. Current evidence guiding red-cell transfusion in patients with subarachnoid hemorrhage is limited, conflicting, and primarily based on small observational studies.[9] Because existing management guidelines regarding transfusion strategies in these patients offer vague recommendations to maintain hemoglobin levels within the normal range or to transfuse in the case of anemia, the appropriate transfusion threshold remains unknown.[10] Consequently, this common clinical problem has been identified as a priority evidence gap to be addressed.[11,12] We conducted the Subarachnoid Hemorrhage Red Cell Transfusion Strategies and Outcome (SAHARA) trial to test the hypothesis that a liberal red-cell transfusion strategy, as compared with a restrictive red-cell transfusion strategy, improves neurologic outcomes at 12 months.

METHODS

TRIAL DESIGN AND OVERSIGHT

This was an investigator-initiated, pragmatic, open-label, randomized trial with a blinded outcome assessment. The trial was conducted at 23 centers specializing in neurocritical care with neurosurgical and neurointerventional support in Canada, Australia, and the United States. The trial was funded by peer-reviewed grants from funding agencies of the Canadian and Australian governments. The funders had no input into the trial design, data analysis and interpretation, or writing of the manuscript. The Ottawa Methods Centre of the Ottawa Hospital Research Institute coordinated the trial with a regional coordination center at the George Institute for Global Health. The trial was overseen by the trial executive and steering committees. Approval from a research ethics board at each site was obtained, and the trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation. Regional remote monitoring was conducted in accordance with the monitoring plan. An independent data and safety monitoring board reviewed the fidelity of the trial to the protocol and safety metrics twice yearly and reviewed safety and efficacy at a single interim analysis. An internal pilot trial (ClinicalTrials.gov number, NCT02483351) to establish feasibility preceded the full trial, with all outcomes from the pilot trial reported along with those from the full trial without interim analysis.[13] The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. A priori and consent-to-continue (delayed) consent were used in accordance with local research ethics board approvals. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The writing committee drafted the manuscript, and all the authors reviewed and approved submission of the manuscript for publication.

PATIENTS

Patients 18 years of age or older with a first-ever aneurysmal subarachnoid hemorrhage and a hemoglobin level of 10.0 g per deciliter or lower within the first 10 days after admission were eligible. In the pilot trial, the eligibility period was within the first 14 days after admission, which was the only substantive protocol change in the transition to the full trial. Patients were excluded if they had nonaneurysmal subarachnoid hemorrhage, active bleeding leading to hemodynamic instability, or contraindications or known objections to blood transfusion. Full eligibility criteria are described in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND INTERVENTION

Eligible patients were randomly assigned in a 1:1 ratio to a liberal transfusion strategy or a restric-

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tive transfusion strategy with the use of a central, concealed, computer-generated sequence with variable permuted blocks of four and six stratified according to center. In the liberal-strategy group, transfusions were mandatory at a hemoglobin level of 10 g per deciliter or less. This threshold was informed by physician preference,[14] physiological evidence of brain-tissue hypoxia and metabolic distress below this threshold,[15] and data showing improved oxygen delivery[16-18] and oxygen extraction.[8] In the restrictive-strategy group, transfusions were only permitted at a hemoglobin level of 8 g per deciliter or less. This threshold was informed by a survey of intensivists, neurointensivists, and neurosurgeons and a multicenter observational cohort study.[16-18] Patients received leukoreduced red cells, 1 unit at a time, when the specified hemoglobin threshold was met. The assigned transfusion strategy was applied from the time of randomization to 21 days after the first hospital presentation, death, or hospital discharge, whichever came first. Measurements of hemoglobin level could be performed by the hospital laboratory or by means of point-of-care testing and occurred daily up to day 10 or while the patient was in intensive care. The remainder of patient care was left to the discretion of the treatment team. Adherence by the treatment teams to available practice guidelines was encouraged.[11,12,19,20] Protocol adherence was assessed on the basis of adherence to the assigned transfusion threshold and time to transfusion.

OUTCOMES

The primary outcome was an unfavorable neurologic functional outcome at 12 months, defined as a score of 4 or higher on the modified Rankin scale. The modified Rankin scale is an ordinal scale that measures neurologic function (scores range from 0 [full recovery] to 6 [death], with a score of 5 indicating severe disability), and it is frequently dichotomized in subarachnoid hemorrhage trials.[21] Secondary patient-reported outcomes at 12 months were the Functional Independence Measure (FIM; scores range from 18 to 126) and quality of life measured by the EuroQol five-dimension, five-level (EQ-5D-5L) utility index (scores range from −0.1 to 0.95) and visual analogue scale (VAS) (scores range from 0 to 100), with higher scores on each assessment indicating better health status or quality of life. Questionnaires regarding the modified Rankin scale, FIM, and EQ-5D-5L were answered by the patient or their proxy, with scores centrally obtained by trained assessors who were unaware of trial-group assignments.[22,23] Minimally important differences between the groups have not been established for subarachnoid hemorrhage. Additional secondary outcomes included new vasospasm detected on imaging (radiographic vasospasm) and delayed cerebral ischemia over the first 21 days of hospitalization, and new cerebral infarction as captured on routinely performed cerebral imaging. These outcomes were centrally adjudicated by an assessor, who was unaware of trial-group assignments, with the use of accepted definitions.[24] Full details of the scoring tools used for outcome assessments are provided in the Supplementary Appendix. Tertiary outcomes were the lowest daily hemoglobin levels over the first 21 hospital days, the proportion of patients receiving red-cell transfusion, the need for and duration of mechanical ventilation, length of stay in the critical care unit and in the hospital, and transfusion-related adverse events over the first 28 hospital days.

STATISTICAL ANALYSIS

We estimated that a sample size of 740 patients would provide the trial with 80% power, at a two-sided type I error rate of 0.05 and with a conservative 3% loss to follow-up, to show a 25% relative reduction in the risk of the primary outcome event in the liberal-strategy group, based on the assumption that 40% of the patients in the restrictive-strategy group would have an unfavorable outcome. These estimations were informed by observational data,[25] investigator consensus,[26] and previous trials of other interventions in this population.[27,28]

All the patients were assessed according to the group to which they were assigned, and all analyses were adjusted for center and sex. The primary outcome analysis was performed with the use of a binomial generalized linear mixed model with fixed effects for treatment and sex and a random effect for center with a log-link function to produce a risk ratio. A proportional-odds analysis was also conducted, with the proportional-odds assumption tested with the use of the Brant–Wald test and the full ordinal modified Rankin scale. For secondary outcomes, the FIM, EQ-5D-5L utility index score (Canada value set), and VAS were analyzed with the use of a linear generalized linear mixed model with an identity-

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link function and are reported as mean differences. In addition, we restricted an analysis to survivors only. Other secondary outcomes were analyzed with the use of a log-binomial generalized linear mixed model and reported as risk ratios. The lowest daily hemoglobin levels are presented as means. Tertiary outcomes reported as proportions were analyzed with the use of a log-binomial generalized linear mixed model; continuous variables were analyzed with the use of quantile regression and reported as median differences. Details on the statistical analyses are available in the Supplementary Appendix. Results are presented with 95% confidence intervals. There was no correction for multiplicity when we conducted tests for secondary outcomes or subgroups; the widths of the confidence intervals were not adjusted and should not be used in place of a hypothesis test.

Prespecified subgroups for the primary outcome were assessed for variations in treatment effect according to age (>55 years), sex, clinical severity (as measured by World Federation of Neurological Surgeons grade), radiographic grade (on the modified Fisher Scale), aneurysm securing method (neurosurgical vs. endovascular approach), and presence at baseline of delayed cerebral ischemia or radiographic vasospasm. Prespecified sensitivity analyses of the primary outcome included further adjustment for World Federation of Neurological Surgeons severity score and age, definition of an unfavorable outcome as a score of 3 or higher on the modified Rankin scale, best-case and worst-case scenarios for missing data, and a per-protocol analysis.[29]

The independent data and safety monitoring board reviewed an interim analysis of the primary outcome in the first 370 patients with the use of the Haybittle–Peto stopping rule for type I error control.[30,31] All analyses were performed with the use of SAS software, version 9.4 (SAS Institute); R software, version 4.3.1 (R Foundation for Statistical Computing), was used for proportional-odds analysis, quantile regression, and creation of forest plots.

RESULTS

PATIENTS AND INTERVENTIONS

A total of 60 patients were enrolled in the pilot trial between October 17, 2015, and November 21, 2016, and 682 patients were enrolled in the full trial between March 11, 2018, and July 10, 2023. Of the 742 patients who underwent randomization, 9 declined or withdrew consent and 1 with no next of kin, who was enrolled under the delayed consent provision, died before consent was provided. The local research ethics board disallowed keeping the data of the patient who died. Data regarding the primary outcome were not obtained for 7 patients (0.96%). A total of 364 patients in the liberal-strategy group and 361 patients in the restrictive-strategy group were included in analyses (Fig. S2 in the Supplementary Appendix). A total of 7 patients who were enrolled on day 11 after their first hospital presentation (a day over the 10-day inclusion window for the full trial) completed the trial and are included in the analysis populations (Table S4).

The baseline characteristics of patients are shown in Table 1 and Table S5. The mean (±SD) age was 59.4±12.3 years, 82% were women, and the incidence of coexisting conditions was similar in the two groups. Patients underwent randomization on median day 3 (interquartile range, 2 to 5) after hospitalization. The clinical and radiographic severity of disease were similar in the two groups. Ruptured aneurysms were more common in the anterior circulation (in 638 patients [87.2%]) and more frequently secured with the use of the endovascular approach (in 443 patients [60.5%]). The representativeness of the trial population is shown in Table S6.

The median duration of the intervention was 17 days (interquartile range, 13 to 18) in the liberal-strategy group and 16 days (interquartile range, 12 to 18) in the restrictive-strategy group. The mean minimum daily hemoglobin level from the time of randomization is shown in Figure 1; the mean minimum daily hemoglobin level from the first hospital day is shown in Figure S3. The median pretransfusion hemoglobin level in the liberal-strategy group was 9.6 g per deciliter (interquartile range, 9.4 to 9.8) and 7.6 g per deciliter (interquartile range, 7.2 to 7.8) in the restrictive-strategy group. The median time from hemoglobin measurement to transfusion was 6.1 hours (interquartile range, 4.0 to 8.5) in the liberal-strategy group and 4.4 hours (interquartile range, 2.4 to 7.1) in the restrictive-strategy group. There were 12 protocol violations affecting 11 patients (1.5%) — 8 violations (2.2%) in the liberal-strategy group and 4 violations (0.9%) in the restrictive-strategy group. Detailed protocol adherence metrics are

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Table 1. Characteristics of the Patients at Baseline.*

Variable	Liberal Strategy (N=366)	Restrictive Strategy (N=366)
Age — yr		
Mean	59.3±12.5	59.5±12.2
Median (IQR)	60 (51–68)	60 (52–68)
Sex — no. (%)		
Female	299 (81.7)	299 (81.7)
Male	67 (18.3)	67 (18.3)
Relevant medical history — no. (%)		
Hypertension	161 (44.0)	177 (48.4)
Current or previous smoker	123 (33.6)	149 (40.7)
Ischemic heart disease	3 (0.8)	3 (0.8)
Congestive heart failure	15 (4.1)	28 (7.7)
History of intracranial hemorrhage	1 (0.3)	5 (1.4)
Ischemic stroke	7 (1.9)	14 (3.8)
End-stage renal disease	1 (0.3)	0
Chronic anemia	20 (5.5)	23 (6.3)
No. of days from first hospital presentation to randomization		
Mean	3.6±2.2	3.8±2.5
Median (IQR)	3 (2–5)	3 (2–5)
Median score on the World Federation Neurological Surgeons scale at admission (IQR)†	3 (1–4)	3 (1–4)
Median score on the modified Fisher scale (IQR)‡	4 (3–4)	4 (3–4)
Externalized ventricular drain — no. (%)	257 (70.2)	255 (69.7)
Location of aneurysm — no. (%)		
Anterior circulation	328 (89.6)	310 (84.7)
Posterior circulation	38 (10.4)	56 (15.3)
Aneurysm treatment — no. (%)§		
Endovascular	218 (59.6)	225 (61.5)
Neurosurgical	151 (41.3)	140 (38.3)
No treatment	5 (1.4)	6 (1.6)
Median no. of days from first hospitalization to first aneurysm treatment (IQR)	1 (0–1)	1 (0–1)
Presence of delayed cerebral ischemia or radiographic vasospasm — no. (%)		
Delayed cerebral ischemia	50 (13.7)	57 (15.6)
Radiographic vasospasm	134 (36.6)	128 (35.0)
Vasopressor or inotropic therapy — no. (%)	180 (49.2)	155 (42.3)
Previous red-cell transfusion — no. (%)	40 (10.9)	28 (7.7)
Hemoglobin level at randomization — g/dl		
Mean	9.4±0.6	9.3±0.6
Median (IQR)	9.5 (9.1–9.8)	9.5 (9.0–9.8)

* Plus–minus values are means ±SD. IQR denotes interquartile range, and SAH subarachnoid hemorrhage.
† The basis of scores on the World Federation of Neurological Surgeons scale is as follows: 1, Glasgow Coma Scale (GCS) score of 15; 2, GCS score of 13–14 and no focal deficit; 3, GCS score of 13–14 and presence of focal deficit; 4, GCS score of 7–12; and 5, GCS score of less than 7.
‡ The basis of scores on the modified Fisher scale is as follows: 0, no subarachnoid hemorrhage or intraventricular hemorrhage; 1, thin diffuse or focal subarachnoid hemorrhage and no intraventricular hemorrhage; 2, thin diffuse or focal subarachnoid hemorrhage with intraventricular hemorrhage; 3, thick focal (>1 mm) or diffuse subarachnoid hemorrhage and no intraventricular hemorrhage; and 4, thick focal (>1 mm) or diffuse subarachnoid hemorrhage with intraventricular hemorrhage.
§ Data are missing for one patient in the liberal-strategy group.

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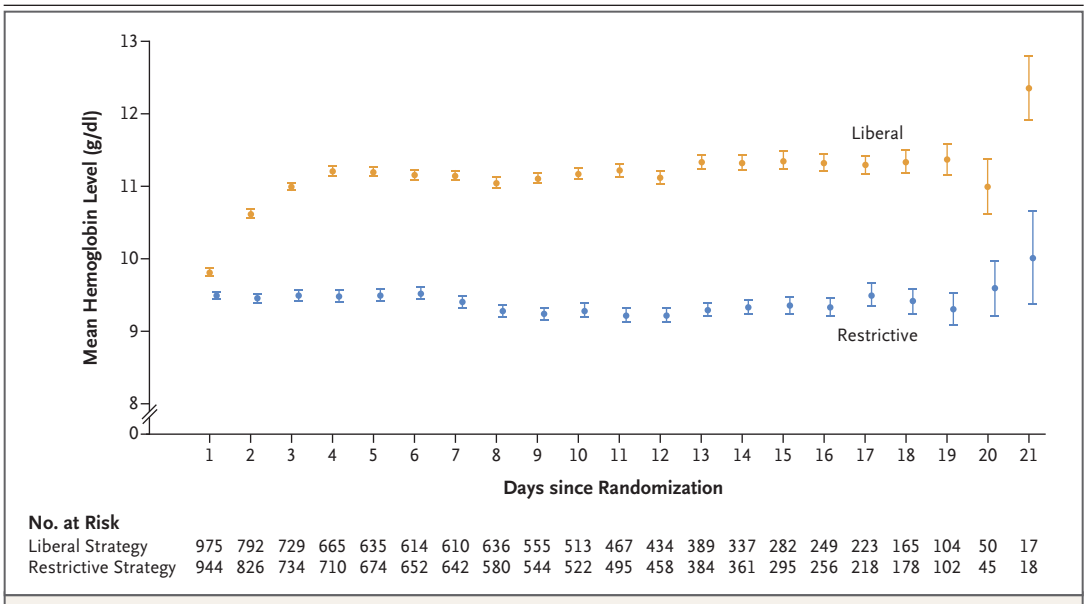

Figure 1. Minimum Daily Hemoglobin Levels from Randomization through Day 21.
I bars indicate 95% confidence intervals.

shown in Table S7. Summaries of cointerventions after randomization are provided in Table S8 and Figure S4.

PRIMARY OUTCOME

An unfavorable neurologic functional outcome (modified Rankin scale score, ≥4) at 12 months was observed in 122 of 364 patients (33.5%) in the liberal-strategy group and in 136 of 361 patients (37.7%) in the restrictive-strategy group (risk ratio, 0.88; 95% confidence interval [CI], 0.72 to 1.09; P=0.22) (Table 2). The distribution of scores on the modified Rankin scale across the two groups is shown in Figure 2. Using a proportional-odds model, we calculated that the odds ratio for patients in the liberal-strategy group having a worse functional outcome score on the modified Rankin scale than the patients in the restrictive-strategy group was 0.82 (95% CI, 0.64 to 1.06). These findings appear to be consistent across sensitivity analyses and subgroup analyses (Fig. S5).

SECONDARY OUTCOMES

Secondary outcomes are shown in Table 2. At 12 months, the mean total FIM score was 82.8±54.6 in the liberal-strategy group and 79.8±54.5 in the restrictive-strategy group (mean difference, 3.01; 95% CI, −5.49 to 11.51). The EQ-5D-5L mean utility index score was 0.5±0.4 in both groups (mean difference, 0.02; 95% CI, −0.04 to 0.09). The VAS mean score was 52.1±37.5 in the liberal-strategy group and 50±37.1 in the restrictive-strategy group (mean difference, 2.08; 95% CI, −3.76 to 7.93). These findings did not differ when data from patients who died were removed (Table 2). Mortality at 12 months was 27.2% in the liberal-strategy group and 27.1% in the restrictive-strategy group (risk ratio, 0.99; 95% CI, 0.77 to 1.28). Radiographic vasospasm was observed in 31.5% of the patients in the liberal-strategy group and 40.7% of the patients in the restrictive-strategy group (risk ratio, 0.77; 95% CI, 0.63 to 0.95). The incidence of delayed cerebral ischemia and new cerebral infarction was similar in the two groups (Table 2).

TERTIARY OUTCOMES

Tertiary outcomes are shown in Table S9. Red-cell transfusions were received by 99.7% of the patients in the liberal-strategy group and 34.9% of the patients in the restrictive-strategy group. Patients in the liberal-strategy group received a median of 2 units of red cells (interquartile range, 2 to 4), as compared with 0 units (interquartile range, 0 to 1) in the restrictive-strategy group (median difference, 2.0; 95% CI, 1.78 to 2.20). The duration of mechanical ventilation, length of stay in the intensive care unit, and length of hospital stay were similar in the two groups.

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Table 2. Outcomes.*

Outcome	Liberal Strategy (N=366)	Restrictive Strategy (N=366)	Risk Ratio or Odds Ratio (95% CI)	Mean Difference (95% CI)
Primary outcome: unfavorable neurologic outcome at 12 mo†				
Principal analysis — no./total no. (%)	122/364 (33.5)	136/361 (37.7)	0.88 (0.72 to 1.09)‡	
Proportional odds			0.82 (0.64 to 1.06)§	
Secondary outcomes				
Functional Independence Measure score¶				
Total score, all patients	82.8±54.6	79.8±54.5		3.01 (–5.49 to 11.51)
Motor subscore	60.2±40.1	57.7±40.2		2.48 (–3.77 to 8.74)
Cognitive subscore	22.6±14.9	22.1±14.8		0.52 (–1.79 to 2.84)
Total score, surviving patients	114.1±23.2	110.2±27.1		3.84 (–0.78 to 8.47)
Motor subscore	82.9±18.1	79.7±21.7		3.19 (–0.48 to 6.86)
Cognitive subscore	31.2±6.3	30.5±6.7		0.65 (–0.54 to 1.85)
EQ-5D-5L utility index‖				
All patients	0.5±0.4	0.5±0.4		0.02 (–0.04 to 0.09)
Nonsurvivors removed	0.8±0.2	0.7±0.3		0.03 (–0.01 to 0.08)
Visual analogue scale score**				
All patients	52.1±37.5	50±37.1		2.08 (–3.76 to 7.93)
Nonsurvivors removed	71.9±22.6	69.6±23.3		2.32 (–1.93 to 6.56)
Death — no./total no. (%)				
In-hospital	74/366 (20.2)	70/366 (19.1)	1.05 (0.77 to 1.44)	
At 12 mo	99/364 (27.2)	98/361 (27.1)	0.99 (0.77 to 1.28)	
New cerebral infarction — no./total no. (%)	58/365 (15.9)	65/366 (17.8)	0.89 (0.63 to 1.26)	
New DCI — no./total no. (%)	64/365 (17.5)	73/366 (19.9)	0.88 (0.64 to 1.21)	
New radiographic vasospasm — no./total no. (%)	115/365 (31.5)	149/366 (40.7)	0.77 (0.63 to 0.95)	

* Plus–minus values are means ±SD. The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. CI denotes confidence interval, and DCI delayed cerebral ischemia.

† For purposes of the primary outcome, an unfavorable neurologic outcome was defined as a modified Rankin scale score of 4 or higher measured at 12 months in a blinded fashion by an independent assessor. Scores on the modified Rankin scale are as follows: 0, complete recovery; 1, no significant disability despite symptoms; 2, slight disability (unable to carry out previous activities but able to look after own affairs); 3, moderate disability (help needed but walks without assistance); 4, moderately severe disability (unable to walk unassisted or to address own bodily needs); 5, severe disability (incontinence and total nursing care); and 6, dead.

‡ P=0.22.

§ Value shown is an odds ratio for the primary outcome.

¶ The Functional Independence Measure score, measured at 12 months in a blinded fashion by an independent assessor, consists of 18 items that assesses 13 different motor and 5 cognitive tasks each measured on an 8-point scale, with a total score range from 18 (complete dependence) to 126 (complete independence).

‖ The EuroQol five-dimension, five-level (EQ-5D-5L) utility index, measured at 12 months in a blinded fashion by an independent assessor, consists of a short and simple five-part questionnaire that is reported as an indexed value and a visual analogue scale. The index value was calculated using the Canadian EQ-5D-5L value set, which ranges from –0.1 (the worst health status) to 0.95 (the best health status).

** The visual analogue scale measures patient-reported perceived health-related quality of life at the time of the response; scores range from 0 to 100, with higher scores indicating better health.

SAFETY AND ADVERSE EVENTS

The incidence of acute transfusion reactions and prespecified adverse events was similar in the two groups (Table S10). There were no unexpected adverse events.

DISCUSSION

In this trial, we did not observe a significant difference in the risk of an unfavorable outcome (a score of ≥4 on the modified Rankin scale) at

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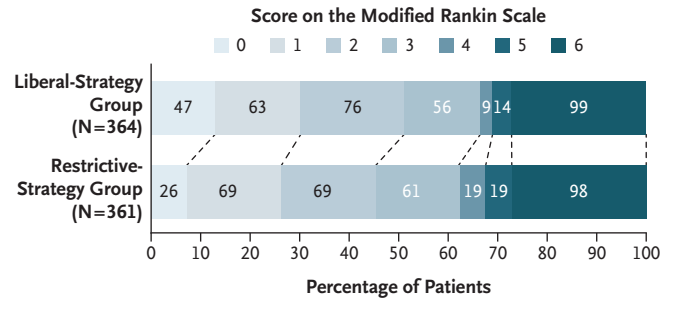

Figure 2. Functional Neurologic Outcome at 12 Months.

12 months between a strategy of liberal red-cell transfusion and a strategy of restrictive use of red-cell transfusion in adult patients with aneurysmal subarachnoid hemorrhage and anemia. This observation was consistent in sensitivity analyses of the primary outcome, across subgroups, and for secondary outcomes. There was no clinically meaningful between-group difference in the incidence of adverse events or reactions to transfusion.

Two recent large, multicenter trials evaluating red-cell transfusion practices in neurocritically ill patients had important differences from our trial. [32,33] Both trials used a different scale to assess neurologic function (Glasgow Outcome Scale–Extended) in a shorter time frame (6 months). Findings from one trial involving 742 patients with moderate and severe traumatic brain injury and anemia showed that there was no significant difference in the risk of unfavorable functional neurologic outcome at 6 months with a liberal transfusion strategy (transfusion at a hemoglobin level of ≤10 g per deciliter) as compared with a restrictive strategy (transfusion at a hemoglobin level of ≤7 g per deciliter).[32] The other trial conducted in a heterogeneous neurocritically ill population, in which 190 patients with subarachnoid hemorrhage represented 23% of the total sample size of 820 patients, showed a reduction in unfavorable neurologic outcomes with a different liberal strategy (threshold hemoglobin level for transfusion, <9 g per deciliter [vs. <10 g per deciliter in our trial]) as compared with a restrictive strategy (threshold hemoglobin level, <7 g per deciliter [vs. <8 g per deciliter in our trial]).[33]

Our trial has several strengths. We ensured the fidelity of our intervention and maintained different hemoglobin levels between the groups throughout the trial period. We minimized potential sources of bias with the use of allocation concealment, central, blinded outcome ascertainment, and adjudication of secondary clinical outcomes. We followed patients for 12 months with minimal loss to follow-up.

Our trial also has limitations. Given the nature of the intervention, it was impractical for the clinical team to be unaware of the trial interventions. This potential source of bias was minimized with centralized, blinded outcome assessment conducted with the use of validated tools,[22] as has been done in several previous trials involving patients with stroke.[34-36] The ascertainment of important secondary outcomes, such as delayed cerebral ischemia, radiographic vasospasm, and new cerebral infarction is challenging in the setting of a clinical trial. Definitions overlap and the pathophysiological features are not fully understood.[37] We addressed this challenge with central and blinded adjudication of these outcomes, relying on the best information provided by the participating sites.

Although the findings from our trial do not show a significant difference between the liberal and restrictive strategies, the possibility of smaller differences in benefit or harm that may be meaningful to patients and families is not excluded. Further meta-analyses of randomized trials may provide additional insight into appropriate practice. In addition, refining patient-centered outcome measures to capture functional improvements is an important consideration for future studies in this population, especially when mortality benefit is unlikely. Considerable progress has been made in establishing new patient-informed outcome measures,[38,39] standardization of data capture in subarachnoid hemorrhage trials,[40] and identification of a core outcome set that reflects the priorities of all involved parties.[41,42] The use of more refined and granular measures of patient-centered outcomes along with sophisticated statistical analysis may allow future trials to identify improvements in outcomes that are important to patients and their families.

Our results show that in patients with aneurysmal subarachnoid hemorrhage and anemia, a liberal strategy of red-cell transfusion over the first 21 days of hospitalization did not result in a lower risk of an unfavorable neurologic outcome at 12 months than a restrictive strategy.

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APPENDIX

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